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	First Named Inventor	Caldwell, Larry
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Address to: Mail Stop AF Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Group Art Unit	1611
	Examiner Name	Ghali, Isis A. D.
	Title: *Methods and compositions for treating headache pain with topical NSAID compositions*	

Sir:

This Brief is filed in support of Appellants' appeal from the Examiner's Rejection dated November 4, 2008. No claims have been allowed. Claims 1-18 and 24-33 are pending and appealed herein. A Notice of Appeal was filed on February 11, 2009.

The Board of Appeals and Interferences has jurisdiction over this appeal pursuant to 35 U.S.C. §134.

The Commissioner is hereby authorized to charge deposit account number 50-0815, reference no. TOPI-002CIP to cover the fee required under 37 C.F.R. §41.20(b)(2) for filing Appellants' Brief. In the unlikely event that the fee transmittal or other papers are separated from this document and/or other fees or relief are required, Appellants petition for such relief, including extensions of time, and authorize the Commissioner to charge any fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 which may be required by this paper, or to credit any overpayment, to deposit account number 50-0815, reference no. TOPI-002CIP.

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REAL PARTY IN INTEREST

The inventors named on this patent application assigned their entire rights to the invention to Topiceutical, Inc.

RELATED APPEALS AND INTERFERENCES

There are currently no other appeals or interferences known to Appellants, the undersigned Appellants' representative, or the assignee to whom the inventors assigned their rights in the instant case, which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal.

STATUS OF CLAIMS

The present application was filed on December 26, 2001 with Claims 1-23. During the course of prosecution, Claims 24-33 were added, and Claims 19-23 were canceled. Accordingly, Claims 1-18 and 24-33 are pending and under examination in the present application, all of which are appealed herein.

STATUS OF AMENDMENTS

No amendments to the Claims were filed subsequent to issuance of the Final Rejection.

SUMMARY OF CLAIMED SUBJECT MATTER

The claimed invention is drawn to methods of treating headache pain caused by a migraine headache, indomethacin responsive headache syndrome, tension headache, or cluster headache by topically applying an anti-inflammatory effective amount of a topical NSAID formulation to a keratinized skin surface of the head of a host to ameliorate the headache pain.

Below is a description of each independent and separately argued independent appealed claim and where support for each can be found in the specification.

Claim 1 claims a method for ameliorating headache pain caused by a tension headache, migraine headache, indomethacin responsive headache syndrome or cluster headache, the method consisting of topically applying an anti-inflammatory effective amount of a topical NSAID formulation comprising an NSAID as the only active agent present in the

topical formulation to a keratinized skin surface of the head of the host to ameliorate the headache pain caused by a migraine headache, indomethacin responsive headache syndrome, tension headache, or cluster headache (see, e.g., p. 2, lines 14-20; p. 4, lines 9-20; p. 5, line 17 to p. 6, line 6; p. 7, lines 9-18; p. 8, lines 10-13).

Claim 27 depends from Claim 1 and further specifies that the headache pain is the result of an Indomethacin Responsive Headache Syndrome and the topical NSAID formulation is indomethacin (see, e.g., p. 5, lines 2-4; p. 8, lines 10-13).

Claim 29 depends from Claim 1 and further specifies that the amount of active NSAID in the topical formulation ranges from about 0.1 to about 5.0% w/w (see, e.g., p. 5, lines 18-22; and p. 8, lines 25-28).

Claim 30 depends from Claim 29 and further specifies that the amount of active NSAID in the topical formulation ranges from about 0.5 to about 3.0% w/w (see, e.g., p. 5, lines 18-22; and p. 8, lines 25-28).

Claim 31 depends from Claim 1 and further specifies that the method results in no toxic side effects which are observed in system NSAID delivery mechanisms (see, e.g., p. 7, lines 19-20).

Independent Claim 6 claims a method of treating a mammal suffering from headache pain caused by a migraine headache, indomethacin responsive headache syndrome, tension headache, or cluster headache, the method consisting of topically applying an anti-inflammatory effective amount of a nonsalicylate NSAID formulation comprising an NSAID as the only active agent present in the topical formulation to a keratinized skin surface of at least one of the forehead and temples of the mammal for a period of time sufficient for amelioration of the headache pain caused by a tension headache, migraine headache, indomethacin responsive headache syndrome or cluster headache to occur (see, e.g., p. 2, lines 14-20; p. 4, lines 9-20; p. 5, line 11 to p. 6, line 6; p. 7, lines 9-18; p. 8, lines 10-13).

Independent Claim 11 claims a method for treating a human suffering from headache pain caused by a migraine headache, indomethacin responsive headache syndrome, tension headache, or cluster headache, the method consisting of topically applying an anti-inflammatory effective amount of a nonsalicylate NSAID formulation comprising an NSAID as the only active agent present in the topical formulation to at least one of the forehead, temples and/or occipital region of the human to at least reduce the pain caused by a migraine headache, indomethacin responsive headache

syndrome, tension headache, or cluster headache (see, e.g., p. 2, lines 14-20; p. 4, lines 9-20; p. 5, line 11 to p. 6, line 6; p. 7, lines 9-18; p. 8, lines 10-13).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

I. Claims 1-18 and 24-33 stand rejected under 35 U.S.C. §103(a) as being obvious over the combined teachings of either Pradalier et al. ("Migraine and non-steroidal anti-inflammatory agents"; Pathol Biol (Paris), 1992 Apr; 40(4):397-405) or Cluff ("Migraine Treatment", International Association for the study of pain, Technical Corner from IASP Newsletter, 1999) each combined with both US 6,667,799 to Caldwell and US 5,318,960 to Toppo.

ARGUMENT

I. Claims 1-18 and 24-33 are patentable under 35 U.S.C. §103(a) over the combined teachings of either Pradalier et al. or Cluff, each combined with both US 6,667,799 to Caldwell and US 5,318,960 to Toppo.

In the arguments set forth below, the Appellants will argue the rejected claims in Groups as follows:

Group I: *Claims 1-18, 24-26, 28, and 32-33*
Group II: *Claim 27*
Group III: *Claims 29-30*
Group IV: *Claim 31*

Group I: *Claims 1-18, 24-26, 28, and 32-33*

As described above, the rejected claims are drawn to methods for treating headache pain caused by a migraine headache, indomethacin responsive headache syndrome, tension headache, or cluster headache, the method consisting of topically applying an anti-inflammatory effective amount of a topical NSAID formulation comprising an NSAID as the only active agent present in the topical formulation to a keratinized skin surface of the head of the host to ameliorate the headache pain caused by a migraine headache, indomethacin responsive headache syndrome, tension headache, or cluster headache. Those skilled in the art understand that “topical“administration of a pain

medication produces subtherapeutic blood levels and thus is not producing its therapeutic effect by acting in the central nervous system but rather have their mechanism of action locally under the skin application site within the soft tissues and local peripheral nerves. This is in contradistinction to "transdermal" administration of pain medication, where the drug is also applied on the skin but the mechanism of action is via therapeutic blood levels and thus the drug acts within the central nervous system.

In order to meet its burden in establishing a rejection under 35 U.S.C. §103, the Office must first demonstrate that a prior art reference, or references when combined, teach or suggest all claim elements. See, e.g., KSR Int'l Co. v. Teleflex Inc., 127 S.Ct. 1727, 1740 (2007); Pharmastem Therapeutics v. Viacell et al., 491 F.3d 1342, 1360 (Fed. Cir. 2007); MPEP § 2143(A)(1). In addition to demonstrating that all elements were known in the prior art, the Office must also articulate a reason for combining the elements. See, e.g., KSR at 1741; Omegaflex, Inc. v. Parker-Hannifin Corp., 243 Fed. Appx. 592, 595-596 (Fed. Cir. 2007) citing KSR. Further, the Supreme Court in KSR also stated that that "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions." KSR at 1740; emphasis added. As such, in addition to showing that all elements of a claim were known in the prior art and that one of skill had a reason to combine them, the Office must also provide evidence that the combination would be a predicted success.

The Office has rejected the claims of this Group as being obvious over the combined teachings of either Pradalier et al. or Cluff, each combined with both US 6,667,799 to Caldwell and US 5,318,960 to Toppo. In making this rejection, the Office asserts that the combination of either Pradalier et al. or Cluff, each combined with both US 6,667,799 to Caldwell and US 5,318,960 to Toppo teaches or suggests every element of the claims.

For the reasons detailed below, the Appellants submit that the combination of references fails to make obvious the rejected claims. Specifically, the Appellants submit that the combination of either Pradalier et al. or Cluff, each combined with Caldwell '799 and Toppo '960, fail to teach or suggest the methods for treating headache pain caused by a migraine headache, indomethacin responsive headache syndrome, tension headache, or cluster headache, consisting of topically applying a NSAID formulation comprising an NSAID as the only active agent present in the topical formulation to a keratinized skin surface of the head of the host, as is claimed.

In the Final Office Action of November 4, 2008, the Office asserts that Pradalier and Cluff teach the use of oral NSAIDs including ibuprofen for treatment of migraine. However, the Office acknowledges that neither reference explicitly teaches topical application of NSAIDs. The Office therefore cites Toppo '960 for NSAIDs applied to the skin of a patient for delivering a pain-relieving substance directly to an afflicted area of the body, but without mention of headache. The Office also cites Caldwell '799 for teaching treatment of a host suffering from headache pain with topical application of a local anesthetic applied to keratinized skin proximal to target nerves associated with headache pain, to provide headache pain relief (Final Office Action, p. 4).

The Office therefore concludes that at the time of the invention, NSAIDs were known to be effective for treatment of headache pain as taught by Pradalier and Cluff; that NSAIDs were known to be delivered topically at a site of pain as taught by Toppo '960; and it was known that migraine could be treated by topical delivery of local anesthetic agents to keratinized skin proximal to target nerves associated with migraine as taught by Caldwell '799. The Office asserts that it would have been obvious to one of skill in that art to treat migraine using NSAIDs as disclosed by Pradalier or Cluff, delivered topically to the site of pain as taught by Toppo '960, to provide pain relief as disclosed by Caldwell '799.

The Appellants respectfully disagree, and contend that the combined references do not teach or suggest all the elements of the rejected claims, as the Office suggests. Furthermore, the Appellants, headache and pain authorities, found their clinical results unexpected and surprising, as they (and all other clinicians) believed NSAIDs would not work topically and were only therapeutic if producing significant systemic levels.

As discussed above, the rejected claims specify *topically applying* an anti-inflammatory effective amount of a topical NSAID formulation to a keratinized skin surface of the head. "Topical" drug products are understood by those of skill in the art to be products that produce their clinical effect by being applied to the skin, which subsequently interact with soft tissues and nerves underlying the keratinized skin where the drug is applied. It is known by those of ordinary skill in the art that topically

applied formulations do not result in clinically significant systemic blood levels, and do not produce any significant systemic side effects.[1]

The rejected claims further specify that *a non-steroidal anti-inflammatory (NSAID) agent* is *the only active agent* present in the topical formulation (i.e., there is no nerve blocking agent present).

The claims also specify that the method is a method for ameliorating headache pain caused by *migraine headache, indomethacin responsive headache syndrome, a tension headache, or cluster headache* (i.e., headaches caused by disturbances in the central nervous system). As stated in the previously submitted declaration by Dr. Bradley Galer dated June 2, 2006,

> "In contrast, headaches such as migraine, cluster, tension headaches, and indomethacin responsive headaches (IRH) are not caused by musculoskeletal or peripheral nerve damage mechanisms, rather they are headaches that are caused by disturbances in the central nervous system [2]...Accordingly, migraine, cluster, tension headache, and IRH conditions are considered unique clinical entities distinct from those conditions of headache pains caused by localized musculoskeletal mechanisms (e.g., muscle contractions). In fact, the International Association for the Study of Pain, the world's foremost medical and scientific pain society characterizes migraine headaches as arising from central nervous system mechanisms, and not the musculoskeletal system." [3]

As such, the rejected claims require topically applying an anti-inflammatory effective amount of a topical NSAID formulation (not a nerve blocking agent) to a keratinized skin surface of the head, which work via a local anti-inflammatory mechanism (i.e., non-systemic), and is applied at a topical site which is not the site of origin of the painful condition, the brain.

The Appellants respectfully submit that A) the combined teachings of the references fail to teach or suggest all elements of the claimed methods; B) the cited combination of references fails to provide the requisite predicted success in the

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[1] See Galer and Dworkin, A Clinical Guide to Neuropathic Pain (McGraw-Hill, 2000) p. 57; and Galer BS, Gammaitoni A, Alvarez, N.; Pain; Scientific American Medicine, WebMD, 2001, Chapter 10, Section XIV, p. 22; and Loeser, JD: Bonica's Management of Pain (Galer BS, " Topical Medications " chapter 87; p. 1737) referred to in the Response to Office Action of 7-13-07, pp.8-9).

[2] See Aurora, "Pathophysiology of Migraine Headache" and Dodick, "Indomethacin-responsive Headache Syndromes." from Exhibit A, enclosed in Response to Office Action of 3-30-06.

[3] See Merskey, H, and Bogduk, N. "Classification of Chronic Pain" 2nd Edition, p. 77; submitted as Exhibit B, enclosed in Response to Office Action of 3-30-06.

claimed invention; and C) the cited prior art references have been improperly combined. These elements are discussed individually below.

A) The Appellants maintain that the combination of the references does not render the claimed invention obvious because the combination of the cited references fails to teach or suggest each and every element of the claims.

The cited prior art references of Pradalier and Cluff disclose the general use of oral NSAIDs for the treatment of migraines, a method well known in the art to provide clinically significant systemic NSAID blood levels required in order to achieve relief of headache pain; in fact it is known that a dose-response relationship exists when these drugs are given orally, that is a certain dose of the drug has to be ingested and carried into the blood stream in order to have a headache alleviating effect. Pradalier and Cluff are silent, however, with respect to topically applying a topical NSAID formulation as in the rejected claims. There is no teaching in either reference of topical administration of NSAIDs, nor is there any suggestion of topical administration of an NSAID in either reference.

Toppo is directed to NSAID compositions for relief of pain, and the only specific pain mentioned in Toppo is arthritis pain (col. 1, lines 20-25), where the area of pain experienced is also the exact site of inflammation and pain generation, causing the symptom of pain in the exact same body region. Furthermore, headache and arthritis have distinct underlying pathophysiologies and as such are studied and cared for by very different types of physician specialties, rheumatology and neurology, with distinct diagnostic evaluations and therapies. The compositions of Toppo are delivered transdermally “directly to afflicted areas of the body” (Field of Invention). Toppo only describes a "transdermal delivery method will allow the drugs and/or medicaments to be delivered precisely into the body at specific area of pain” (Summary of Invention), meaning the area of pain origin. Nowhere does Toppo describe applying a topical NSAID to the keratinized skin of the head, nor does Toppo describe use of the compositions to relieve headache of any kind, let alone headache of central nervous system origin. There is no suggestion in Toppo to treat a headache of central nervous system origin by applying a composition topically to the keratinized skin surface of the head, as in the current claims.

Caldwell is directed to a pain relief composition whose active agent is a local anesthetic and with distinct and different specified areas of drug application

(abstract). Caldwell's teaching, therefore, is the treatment of headache using a specific topical *local anesthetic* formulation which penetrates the keratinized skin surface so as to directly interact with underlying specific nerves resulting in nerve impulse conduction blockade in the stated target nerves (col. 2, lines 46-51). *Local anesthetics* are a specific and distinct class of drugs that work by causing a reduction in nerve impulses by binding to sodium channels on the nerve (resulting in "numbness"), whereas NSAIDs reduce inflammation and do not bind to sodium channels. One of ordinary skill in the art would not extrapolate using the locally-applied nerve blocking agent in Caldwell to the teaching of the other references to topically apply an NSAID for treatment of central headaches as in the current claims. Moreover, the site of application of the topical local anesthetic formulation in Caldwell is very specific such that the formulation patented will penetrate the skin in several specific sites as described in the patent so as to interact with the supraorbital nerve and/or suboccipital nerve and thereby resulting in a supraorbital nerve block and/or suboccipital nerve block, each of which are current methods of treating headache pain via needle injection.

Accordingly, the combination of references fails to teach or suggest topically applying a topical NSAID formulation to a keratinized skin surface of the head to treat a headache of central nervous system origin, as claimed.

B) The Appellants further contend that the combination of the cited references fails to provide one of ordinary skill in the art with predicted success in the claimed invention.

The inventors of the present application found the unexpected and surprising results that, contrary to the accepted belief of those of ordinary skill in the art at the time the application was filed, one could treat the pain of *central* headaches, caused by migraine headache, indomethacin responsive headache syndrome, a tension headache, or cluster headache, by applying a *topical* NSAID formulation to a keratinized skin surface of the head.

The Appellants maintain that those of ordinary skill in the art would not have had a reasonable expectation of success in using a topical formulation of an NSAID applied to the keratinized skin surface of the head because (1) it was believed that the underlying pathophysiologic mechanism of migraines, indomethacin-responsive headaches, tension headaches, and cluster headaches were related to abnormalities deep within the brain; (2) it

was known that topical formulations act locally and do not produce any significant drug levels in the systemic circulation nor in the brain; and (3) oral NSAIDs were known to successfully treat headache symptoms only if clinically significant systemic blood levels were achieved, as supported by the declaration provided by Dr. Newman. [4]

The Examiner has discounted Dr. Newman's declaration by alleging that the declaration was directed only to indomethacin responsive headaches and to one specific NSAID (indomethacin), and that therefore the declaration refers only to the "system described in the application and not to the individual claims" (Final Office Action of 11/4/2008, p. 13).

However, the Appellants respectfully disagree. The Appellants maintain that the claims are directed to topically applying an NSAID formulation, and that indomethacin is representative of the class of NSAIDs. Furthermore, as discussed in the previously cited declaration by Dr. Galer, an indomethacin responsive headache is representative of the class of primary headaches, as are migraine, cluster, and tension headaches.[5] In addition, the example cited in the original application demonstrated relief of migraine headache from topical diclofenac applied to the keratinized skin surface of the head.

C) The Appellants further contend that the Office has improperly combined Pradalier, Cluff, Toppo and Caldwell.

The Appellants maintain that the Office has used improper hindsight reasoning based on the disclosure in the Appellant's specification as the motivation to combine the references. The Appellants maintain that the Examiner's reasoning for combining the use of oral NSAIDs to treat migraine (Pradalier and Cluff) with a topical NSAID applied directly to afflicted areas of the body (Toppo) and the use of a local nerve blocking agent applied to the keratinized skin surface of the head to cause a nerve block and thus treat migraine (Caldwell) is not found in the prior art, and has in fact, been improperly derived from the Appellant's specification. As reasoned in the Board of Appeals decision *Ex Parte* Robert J. Saccomanno, (Appeal 2008-4476; decided

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[4] See the declaration of Dr. Lawrence Newman, dated 12-9-02, submitted with the Response to the Office Action of 12-18-2007.

[5] See International Classification of Headache Disorders, 2nd Edition; http://ihs-classification.org/en/; and Dodick , "Indomethacin-responsive Headache Syndromes.", abstract, from Exhibit A, enclosed in Response to Office Action of 3-30-06.

11/ 21/08), "[T]he Examiner has not established that such reason would have been within the knowledge of one of ordinary skill in the art absent the Appellant's disclosure". In fact, as provided in the declaration by Dr. Newman, the Appellants maintain that it was thought that only clinically significant blood levels of any NSAID and indomethacin, for example, could successfully treat a central headache.

Nowhere except in the Appellant's specification is the teaching that a topically applied NSAID can be used to treat the head pain of a central headache such as migraine. Furthermore, there would be no reason that one of ordinary skill in the art at the time of the invention would have used a topical NSAID applied to the keratinized skin surface of the head to treat a headache caused by a disturbance in the central nervous system. In fact, the Appellants maintain that it would not even be possible for one of ordinary skill in the art to use the method of topical application of NSAIDS to the 'afflicted area' as in Toppo to treat a central headache, for example, because this would mean applying the formulations of Toppo at a site of the affliction which is within the central nervous system, e.g., within the brain [6], not to a keratinized skin surface of the head, as in the rejected claims. The pain that derives from arthritis is born directly within the joint and as such is easily conceived to be treated by a properly formulated topical NSAID, whereas as migraine and other centrally derived headache conditions are believed to be caused from abnormalities within the brain and as such, prior to this invention, would have not been conceived to be alleviated by a topical NSAID applied to the keratinized skin of the head.

Therefore, in view of the above discussion, the Appellants contend that the above references have been improperly combined, and furthermore, that the combination of references does not render the current claims obvious.

In light of the above discussion, it is submitted that: A) the combined teachings of the references fail to teach or suggest all elements of the claimed methods; B) the cited combination of references fails to provide the requisite predicted success in the claimed invention; and C) the cited prior art references have been improperly combined. Accordingly the Appellants submit that the combination of either Pradalier

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[6] A documented site of analgesic action of indomethacin in the case of some types of Indomethacin-responsive headaches. See Dodick, "Indomethacin-responsive Headache Syndromes.", p. 24, col. 2, from Exhibit A, enclosed in Response to Office Action of 3-30-06.

et al. or Cluff, each combined with Caldwell '799 and Toppo '960 fails to make obvious the claims of this Group, because the combined references fail to teach or suggest every element of the claims.

Group II: Claim 27

Claim 27, which further depends from Claim 1, specifies that the headache pain is the result of an Indomethacin Responsive Headache Syndrome and the topical NSAID formulation is indomethacin.

As discussed above, the Appellants submit that the combination of either Pradalier et al. or Cluff, each combined with Caldwell '799 and Toppo '960 to fail to teach or suggest the methods for treating headache pain caused by a migraine headache, indomethacin responsive headache syndrome, tension headache, or cluster headache, consisting of topically applying an anti-inflammatory effective amount of a topical NSAID formulation comprising an NSAID as the only active agent present in the topical formulation to a keratinized skin surface of the head of the host, as is claimed.

The Office has included Claim 27 in the rejection, which contain the element that the headache pain is the result of an Indomethacin Responsive Headache Syndrome and the topical NSAID formulation is indomethacin. However, the Office has provided no valid apparent reason for this rejection. The Appellants maintain that none of the cited references teach a method of treating headache pain from an Indomethacin Responsive Headache Syndrome by topically applying a topical NSAID formulation comprising an NSAID as the only active agent present in the topical formulation to a keratinized skin surface of the head of the host.

Furthermore, none of the cited references suggest this element. As discussed above, rejected Claim 27 specifies *topically applying* a topical NSAID formulation to a keratinized skin surface of the head. "Topical" drug products are understood by those of skill in the art to be products that produce their clinical effect by being applied to the skin, which subsequently interact with soft tissues and nerves underlying the keratinized skin where the drug is applied. It is known by those of ordinary skill in the art that topically applied formulations do not result in clinically significant systemic blood levels, and do not produce any significant systemic side effects.

The Appellants maintain that one of ordinary skill in the art would not have had a reasonable expectation of success in using a topical formulation of an NSAID applied to the keratinized skin surface of the head because (1) it was believed that

the underlying pathophysiologic mechanism of migraines, indomethacin-responsive headaches, tension headaches, and cluster headaches were related to abnormalities deep within the brain; (2) it was known that topical formulations act locally and do not produce any significant drug levels in the systemic circulation nor in the brain; and (3) oral NSAIDs were known to successfully treat headache symptoms only if clinically significant systemic blood levels were achieved, as supported by the declaration provided by Dr. Newman.

Furthermore, the Appellants maintain that the Office has not given a specific reason to discount the declaration by Dr. Newman as cited above with respect to the elements of Claim 27. As provided by Dr. Newman, at the time of the invention it was thought by those of ordinary skill in the art that only clinically significant blood levels of any NSAID and indomethacin, for example, could successfully treat a central headache.

Accordingly the Appellants submit that the combination of either Pradalier et al. or Cluff, each combined with Caldwell '799 and Toppo '960 fails to make obvious the claim of Group II, because the combined references fail to teach or suggest every element of the claims.

Group III: Claims 29-30

Claim 29, which further depends from Claim 1, specifies that the amount of active NSAID in the topical formulation ranges from about 0.1 to about 5.0% w/w. Claim 30, which depends from Claim 29, further specifies that the amount of active NSAID in the topical formulation ranges from about 0.5 to about 3.0% w/w.

As discussed above, the Appellants submit that the combination of either Pradalier et al. or Cluff, each combined with Caldwell '799 and Toppo '960 to fail to teach or suggest the methods for treating headache pain caused by a migraine headache, indomethacin responsive headache syndrome, tension headache, or cluster headache, consisting of topically applying a topical NSAID formulation comprising an NSAID as the only active agent present in the topical formulation to a keratinized skin surface of the head of the host, as is claimed.

The Office has included Claims 29 and 30 in the above rejection, which contain the element that the amount of active NSAID in the topical formulation ranges from about 0.1 to about 5.0% w/w. Claim 30, which depends from Claim 29,

further specifies that the amount of active NSAID in the topical formulation ranges from about 0.5 to about 3.0% w/w). However, the Office has provided no valid apparent reason for the rejection of Claims 29 and 30.

The Appellants maintain that only one reference in the cited combined references refer to a non-oral composition of NSAID agents (Toppo '960). However, nowhere does Toppo '960 teach the element of an active NSAID in a topical formulation that ranges from about 0.1 to about 5.0% w/w, or from about 0.5 to about 3.0% w/w. Toppo merely discloses that the composition should contain no more than about 15 mg of pain reliever per 100ml (col. 3, lines17-19), or ten percent by weight (e.g., Examples 1). Additionally, in many of the examples (e.g., Example 5, or Example 20) Toppo teaches more than one active ingredient, in contrast to the current claims which claim an NSAID as the only active agent present in the topical formulation. Therefore, nowhere does Toppo teach the element of an active NSAID in a topical formulation ranges from about 0.1 to about 5.0% w/w, or from about 0.5 to about 3.0% w/w, wherein the NSAID is the only active agent present in the formulation. As the other cited references fail to disclose NSAIDs in a non-oral composition, the combination of references fail to teach this element of the claims.

Furthermore, Toppo fails to suggest this element, because Toppo discloses NSAID compositions for relief of pain, and the only specific pain mentioned in Toppo is arthritis pain (col. 1, lines 20-25). As is known by those of ordinary skill in the art, arthritis as in Toppo, and headache as in the current claims, have distinct underlying pathophysiologies, with distinct diagnostic evaluations and therapies. The compositions of Toppo are therefore formulated for arthritis pain, and are directed for transdermal delivery “directly to afflicted areas of the body” (Field of Invention). There is no teaching or suggestion in Toppo of an active NSAID in a topical formulation ranges from about 0.1 to about 5.0% w/w, or from about 0.5 to about 3.0% w/w, wherein the NSAID is the only active agent present in the formulation for treating a headache of central nervous system origin by applying a composition topically to the keratinized skin surface of the head, as in the current claims.

Accordingly the Appellants submit that the combination of either Pradalier et al. or Cluff, each combined with Caldwell '799 and Toppo '960 fails to make obvious the claims of Group III, because the combined references fail to teach or suggest every element of the claims.

Group IV: Claim 31

Claim 31, which further depends from Claim 1, specifies that the method results in no toxic side effects which are observed in system NSAID delivery mechanisms.

As discussed above, the Appellants submit that the combination of either Pradalier et al. or Cluff, each combined with Caldwell '799 and Toppo '960 to fail to teach or suggest the methods for treating headache pain caused by a migraine headache, indomethacin responsive headache syndrome, tension headache, or cluster headache, consisting of applying a topical NSAID formulation comprising an NSAID as the only active agent present in the topical formulation to a keratinized skin surface of the head of the host, as is claimed.

The Office has included Claim 31 in the rejection, which contain the element that the method results in no toxic side effects which are observed in system NSAID delivery mechanisms. However, the Office has provided no valid apparent reason to reject the claim in this Group.

As discussed above with respect to the Claims in Group III, the Appellants maintain that only reference in the cited combination of references refers to a non-oral composition of NSAID agents (Toppo '960). However, nowhere does Toppo '960 teach the element of a method for treating headache pain caused by a migraine headache, indomethacin responsive headache syndrome, tension headache, or cluster headache, consisting of applying a topical NSAID formulation which results in no toxic side effects seen with systemic therapy. Toppo merely discloses NSAID compositions for relief of pain, and the only specific pain mentioned in Toppo is arthritis pain (col. 1, lines 20-25). There is absolutely no teaching in Toppo of treating headache pain.

Furthermore, Toppo fails to suggest this element, because the only specific pain mentioned in Toppo is arthritis pain. As is known by those of ordinary skill in the art, arthritis and headache have distinct underlying pathophysiologies, with distinct diagnostic evaluations and therapies. The compositions of Toppo are therefore formulated for arthritis pain, and are directed for transdermal delivery “directly to afflicted areas of the body” (Field of Invention). There is no teaching or suggestion in Toppo of a formulation for treating a headache of central nervous system origin by applying a composition topically to the keratinized skin surface of the head, as in the current claims.

Accordingly the Appellants submit that the combination of either Pradalier et al. or Cluff, each combined with Caldwell '799 and Toppo '960 fails to make obvious

the claims of Group IV, because the combined references fail to teach or suggest every element of the claims.

In view of the arguments above, the Appellants submit that the combination of either Pradalier et al. or Cluff, each combined with Caldwell '799 and Toppo '960 fail to teach or suggest all the elements of the rejected claims. Specifically, the Appellants contend that: A) the combined teachings of the references fail to teach or suggest all elements of the claimed methods; B) the cited combination of references fails to provide the requisite predicted success in the claimed invention; and C) the cited prior art references have been improperly combined. Therefore, the combined references do not make obvious the rejected claims. The Appellants therefore respectfully request reversal of this rejection.

SUMMARY

I. Claims 1-18 and 24-33 are patentable under 35 U.S.C. §103(a) over the combined teachings of either Pradalier et al. or Cluff, each combined with both US 6,667,799 to Caldwell and US 5,318,960 to Toppo, because the cited references fail to teach or suggest, either expressly or inherently, the method for treating headache pain caused by a migraine headache, indomethacin responsive headache syndrome, tension headache, or cluster headache, the method consisting of applying an anti-inflammatory effective amount of a topical NSAID formulation comprising an NSAID as the only active agent present in the topical formulation to a keratinized skin surface of the head of the host to ameliorate the headache pain caused by a migraine headache, indomethacin responsive headache syndrome, tension headache, or cluster headache.

RELIEF REQUESTED

The Appellants respectfully request that the rejections of Claims 1-18 and 24-33 under 35 U.S.C. §103 (a) be reversed, and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

Respectfully submitted,

Date: April 13, 2009 By: /Lynn J. Kidder, Reg. No. 56,107/

Lynn J. Kidder
Registration No. 56,107

Date: April 13, 2009 By: /Bret E. Field, Reg. No. 37,620/

Bret E. Field
Registration No. 37,620

Enc.:

- The 1.132 declaration dated 12-9-02 and Curriculum Vitae of Dr. Lawrence C. Newman, filed on 12/10/2002 for the parent application 09/755,592, submitted with the Response to the Final Office Action of 12-18-2007, filed on March 31, 2008.
- The 1.132 declaration of Dr. Bradley S. Galer dated June 2, 2006, filed on 6/26/2006.
- The Curriculum Vitae of Dr. Bradley S. Galer, filed on 1/5/2006.
- Aurora, "Pathophysiology of Migraine Headache"; Dodick, "Indomethacin-responsive Headache Syndromes"; and International Classification of Headache Disorders, 2nd Edition from Exhibit A, enclosed in Response to Office Action of 3-30-06, filed on 6/26/2006.
- Merskey, H, and Bogduk, N. "Classification of Chronic Pain" 2nd Edition, p. 77; submitted as Exhibit B, enclosed in Response to Office Action of 3-30-06, filed on 6/26/2006.
- Galer and Dworkin, A Clinical Guide to Neuropathic Pain (McGraw-Hill, 2000); Galer BS, Gammaitoni A, Alvarez, N.; Pain; Scientific American Medicine, WebMD, 2001, Chapter 10, Section XIV; and Loeser, JD: Bonica's Management of Pain (Galer BS, "Topical Medications" chapter 87; (Lippincott Williams and Wilkins, 2001) submitted in the Response to Office Action of 7-13-07, filed on 10/5/2007.

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CLAIMS APPENDIX

1. A method for ameliorating headache pain caused by a tension headache, migraine headache, indomethacin responsive headache syndrome or cluster headache, said method consisting of:

topically applying an anti-inflammatory effective amount of a topical NSAID formulation comprising an NSAID as the only active agent present in said topical formulation to a keratinized skin surface of the head of said host to ameliorate said headache pain caused by a tension headache, migraine headache, indomethacin responsive headache syndrome or cluster headache.

2. The method according to Claim 1, wherein said topical NSAID formulation comprises a nonsalicylate NSAID.

3. The method according to Claim 1, wherein said topical formulation is a cream.

4. The method according to Claim 1, wherein said topical formulation is a patch.

5. The method according to Claim 1, wherein said host is a mammal.

6. A method of treating a mammal suffering from headache pain caused by a tension headache, migraine headache, indomethacin responsive headache syndrome or cluster headache, said method consisting of:

topically applying an anti-inflammatory effective amount of a nonsalicylate NSAID formulation comprising an NSAID as the only active agent present in said topical formulation to a keratinized skin surface of at least one of the forehead and temples of said mammal for a period of time sufficient for amelioration of said headache pain caused by a tension headache, migraine headache, indomethacin responsive headache syndrome or cluster headache to occur.

7. The method according to Claim 6, wherein said mammal is a human.

8. The method according to Claim 6, wherein said formulation is a cream.

9. The method according to Claim 6, wherein said formulation is a patch.

10. The method according to Claim 6, wherein said keratinized skin surface is selected from the group consisting of the forehead, temple and/or occipital region.

11. A method for treating a human suffering from headache pain caused by a tension headache, migraine headache, indomethacin responsive headache syndrome or cluster headache, said method consisting of:

topically applying an anti-inflammatory effective amount of a nonsalicylate NSAID formulation comprising an NSAID as the only active agent present in said topical formulation to at least one of the forehead, temples and/or occipital region of said human to at least reduce said pain caused by a tension headache, migraine headache, indomethacin responsive headache syndrome or cluster headache.

12. The method according to Claim 11, wherein said NSAID formulation is a cream.

13. The method according to Claim 11, wherein said NSAID formulation is a patch.

14. The method according to Claim 11, wherein said NSAID is an acetic acid.

15. The method according to Claim 14, wherein said NSAID is diclofenac.

16. The method according to Claim 11, wherein said NSAID is indomethacin.

17. The method according to Claim 11, wherein said NSAID is ibuprofen.

18. The method according to Claim 11, wherein said NSAID is ketoprofen.

24. The method according to Claim 1, wherein said topical NSAID formulation consists essentially of an NSAID as the only active agent present in said topical formulation.

25. (Previously Presented) The method according to Claim 1, further comprising determining said host has said headache pain prior to topically applying said nonsalicylate NSAID formulation.

26. The method according to Claim 1, wherein said topical NSAID formulation consists of an NSAID as the only active agent present in said topical formulation.

27. The method of Claim 1, wherein said headache pain is the result of an Indomethacin Responsive Headache Syndrome and said topical NSAID formulation is indomethacin.

28. The method of Claim 1, wherein said headache pain is caused by migraine headache.

29. The method of Claim 1, wherein the amount of active NSAID in said topical formulation ranges from about 0.1 to about 5.0% w/w.

30. The method of Claim 29, wherein the amount of active NSAID in said topical formulation ranges from about 0.5 to about 3.0% w/w.

31. The method according to Claim 1, wherein said method results in no toxic side effects which are observed in system NSAID delivery mechanisms.

32. The method according to Claim 10, wherein said keratinized skin surface is the forehead.

33. The method according to Claim 10, wherein said keratinized skin surface is the temple.

EVIDENCE APPENDIX

The declaration under 37 CFR 1.132 by Dr. Lawrence Newman dated 12-9-02, and the Curriculum Vitae of Dr. Lawrence C. Newman filed on 12/10/2002 for the parent application 09/755,592, submitted with the Response to the Final Office Action of 12-18-2007; the declaration under 37 CFR 1.132 of Dr. Bradley Galer dated June 2, 2006, filed on 6/26/2006; the Curriculum Vitae of Dr. Bradley S. Galer, filed on 1/5/2006; Aurora, "Pathophysiology of Migraine Headache"; Dodick, "Indomethacin-responsive Headache Syndromes"; and International Classification of Headache Disorders, 2nd Edition from Exhibit A, enclosed in Response to Office Action of 3-30-06, filed on 6/26/2006; Merskey, H, and Bogduk, N. "Classification of Chronic Pain" 2nd Edition, p. 77; submitted as Exhibit B, enclosed in Response to Office Action of 3-30-06, filed on 6/26/2006; Galer and Dworkin, A Clinical Guide to Neuropathic Pain (McGraw-Hill, 2000); Galer BS, Gammaitoni A, Alvarez, N.; Pain; Scientific American Medicine, WebMD, 2001, Chapter 10, Section XIV; and Loeser, JD: Bonica's Management of Pain (Galer BS, "Topical Medications" chapter 87; (Lippincott Williams and Wilkins, 2001) submitted in the Response to Office Action of 7-13-07, filed on 10/5/2007 are enclosed as evidence with this Appeal Brief.

RELATED PROCEEDINGS APPENDIX

As stated in the *Related Appeals and Interferences* section above, there are no other appeals or interferences known to Appellants, the undersigned Appellants' representative, or the assignee to whom the inventors assigned their rights in the instant case, which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal. As such this section is left blank.